
بسم الله الرحمن الرحيم
In The Name Of ALLAH
The Most Gracious, The Most Merciful

Armed Forces College of Medicine

AFCM

Endocrine & Urogenital Module

Male & Female Sex Hormones Analogs & Inhibitors 2

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Endocrine & Urogenital Module

INTENDED LEARNING OBJECTIVES (ILO)

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2.

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4.

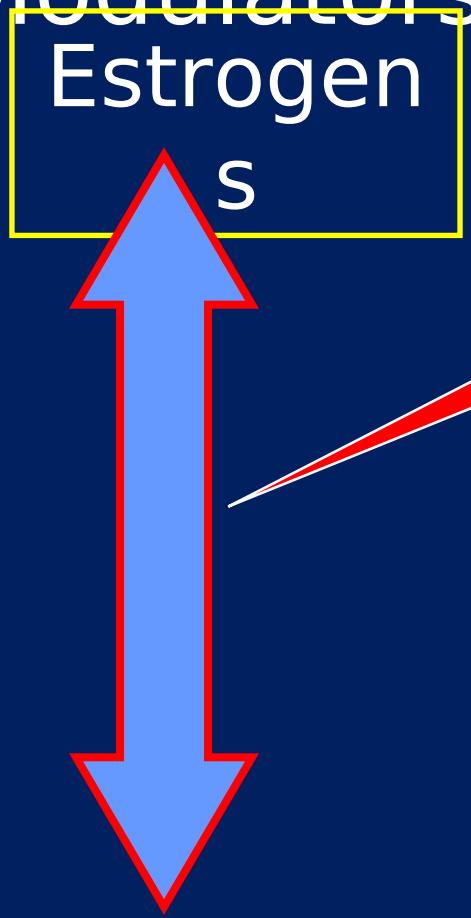
5.

Selective Estrogen Receptor Modulators (SERMs)

SERMs

They are a class of estrogen-related compounds that display selective agonism or antagonism for estrogen receptors depending on the tissue type

Selective Ostrogen Receptor Modulators

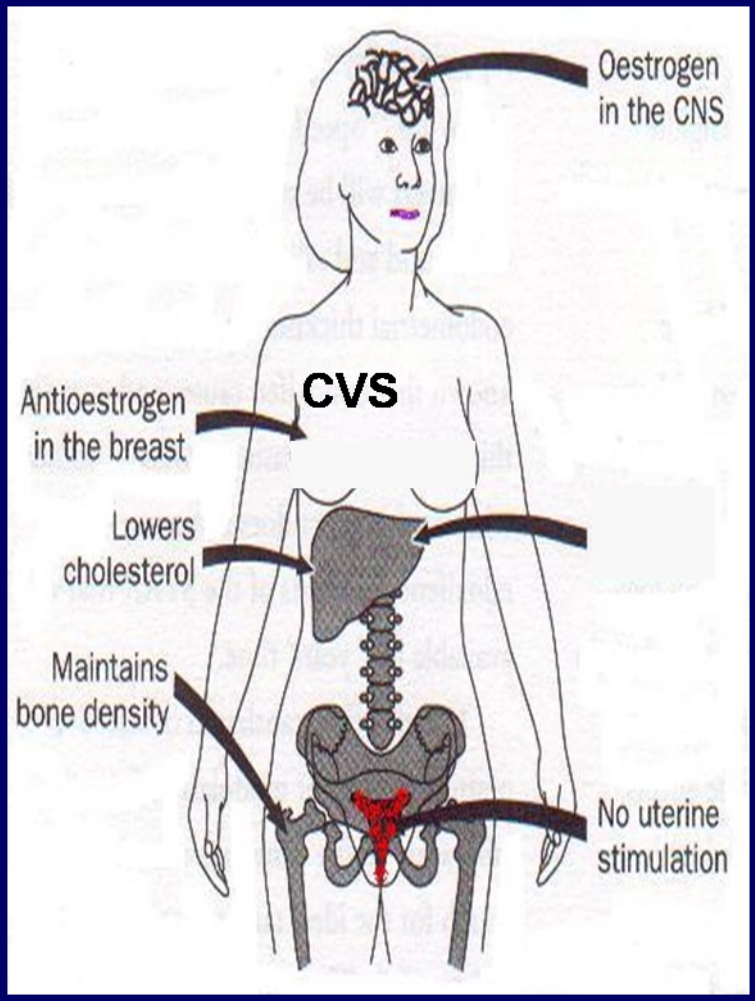


SERMs

SERMs- designed to act in specific ways at each of the oestrogen receptor sites in different tissues

ideal SERM is one that:

- **prevents** bone loss.
- has **no risk** of uterine or breast cancer.
- has **+ve effect** on lipids & cardiovascular system.
- **relieves PMS** & maintains cognitive function of the brain



Adopted from – Rita de Cassia M Dardes

& V Craig Jordan

Tamoxifen

- Selective estrogen receptor modulator (orally)

Indication: Breast Cancer

- in treatment of metastatic Breast Cancer
- adjuvant therapy after mastectomy or radiation

Tamoxifen

- **It is subject to many drug interactions :**
- **Tamoxifen is extensively metabolized by cytochrome P450 isoenzymes, including formation of active metabolites via the CYP3A4/5 and CYP2D6 isoenzymes:**
  - **Patients with a genetic polymorphism in CYP2D6 may produce less active metabolite, resulting in diminished activity of tamoxifen.**
  - **Some CYP450 inhibitors may prevent the formation of active metabolites of tamoxifen and possibly reduce the efficacy (e.g amiodarone, haloperidol, risperidone)**
  - **Tamoxifen is also an inhibitor of CYP3A4 & P-glycoprotein**

Tamoxifen

Adverse effects:

- **hot flushes**

∀↑ **risk of endometrial cancer:**

Due to its estrogenic activity in the endometrium, endometrial hyperplasia and malignancies have been reported with tamoxifen therapy. This has led to recommendations for limiting the length of time on the drug for some indications

- **↑ risk of DVT & pulmonary embolism**

Raloxifene

- Selective estrogen receptor modulator
- No effect on endometrium √ √
- Effective for prevention &ttt of osteoporosis in postmenopausal women
- Reduction in risk of breast cancer :

  Used as prophylactic therapy to reduce the risk of breast cancer in high-risk patients.

Adverse effects:

- Does not relieve PostMenopausal hot flushes

∀ ↑ Risk of venous thromboembolism (high)

Clomiphene Citrate

- **Partial agonist** at estrogen receptors.
- **ovulation-inducing agent.**
- by inhibiting estradiol's negative feedback effect on ant. Pituitary → ↑ **secretion of GnRH & gonadotropins**

→ marked stimulation and enlargement of ovaries & ↑ estrogen secretion & **induction of ovulation.**

- **Clomiphene:** is useful for the treatment of infertility associated with anovulatory cycles.

- **Dosage: 50 mg/ d X 5 days:**
  (+) ovulation → same course repeated until pregnancy occurs

- **Adverse Effects:**
  - hot flushes – most common
  - ovarian enlargement
  - multiple pregnancy – 10%

Pure Estrogen Receptor Antagonists:

Fulvestrant :

It is a pure estrogen receptor antagonist (in all tissues)

It is used in:

The treatment of women with breast cancer

that has developed resistance to

- **Synthesis Inhibitors:**

Aromatase inhibitors

Used in the treatment of breast cancer

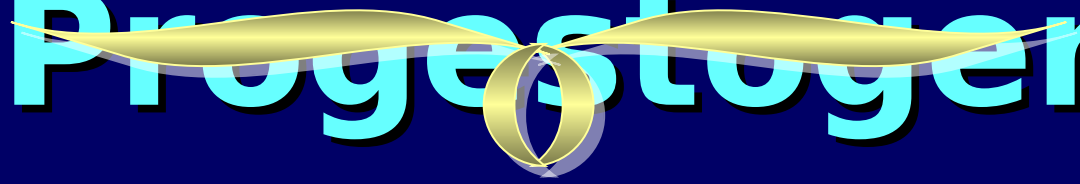
Aromatase:

it is enzyme in the last step in estrogen synthesis

- **Anastrozole** and related compounds **(letrozole)**

Nonsteroidal competitive inhibitors of

Preparations of Progestogens



Progestogens

Secretion:

Mainly by the corpus luteum.

Large amounts by placenta during pregnancy.

Small amounts by :

Adrenal cortex in both sexes.

Testes in males.

- N.B:Progesterone is ineffective orally because it is completely metabolized by the liver through a first pass effect.
- Given IM in oily solutions, very short half-life.

Preparations

Progesterone: 5-10 mg oily sol IM.

May be implanted SC as pellets or microcrystals

Synthetic (Progestins) :

- ***Derivatives of progesterone:***

Medroxyprogesterone acetate:

2.5-10mg daily, orally,

150 mg I.M / 3 months (Depo-Provera).

- ***Derivatives of nortestosterone***

Norethindrone (norethisterone):(Primolut N) 10-30 mg daily orally.

Norgestrel : oral tablets or S.C. Implantation

Pharmacological Actions

1. Together with estrogens, it converts the endometrium to "secretory phase" to prepare it for implantation of fertilized ovum.
2. ↓the sensitivity of the myometrium to oxytocin & cause relaxation of the uterine muscle.
3. Promotes development of the acini and growth of the breast in estrogen primed mammary glands.
4. Inhibition of ovulation (Inhibit LH)
5. Thermogenic effect: at time of ovulation (0.5°C).
6. Progesterone competes with aldosterone at the renal tubule leading to inhibition of Na^+ reabsorption.

Therapeutic uses

1. **Oral contraception**: alone or with estrogen.
2. Postmenopausal hormonal therapy (with estrogen)
3. Dysmenorrhea.
4. Amenorrhea: artificial cycle: estrogen for 25 days with progesterone 15 th - 25th day . Menstruation occurs on withdrawal .
5. Premenstrual tension.
6. Endometriosis.

Side effects

- Weak androgenic actions:

  in progestins derived from testosterone

  (→ hirsutism & acne) .
- ↑ cholesterol → atherosclerosis

Anti - progestogens

Mifepristone

Danazol

Mifepristone

- Potent competitive antagonist of progesterone & glucocorticoid R
- acts as partial agonist if progestin is absent
- Long plasma half-life : 20 to 40 hours
- **Indications:**

1) Medical abortion: during the first trimester

- 400-600mg/day X 4 days or 800 mg/day X 2 days
- **Combination:**

600 mg + PG E1 vaginal pessary or 1 gm. Misoprostol orally

(95% effective during 1st 7 weeks after conception)

- major adverse effect: prolonged bleeding

2) Postcoital contraceptive: prevents implantation

- **Adverse effects:** vomiting, diarrhea, abdominal pain, pelvic pain

Danazol

- Used in treatment of **endometriosis.**

Mechanism:

Inhibits the release of GnRH & gonadotropins ---- inhibits steroid synthesis in the ovary ---- atrophic changes in endometrium.

- **weak agonist** at progestational, androgenic and glucocorticoid Rs.
- Has **weak androgenic effects**.
- Also used in ttt of Menorrhagia & Gynecomastia (in males

Major adverse effects:

weight gain, edema.

↓ breast size, acne & oily skin, ↑ hair growth, deepening o voice headache, hot flushes, muscle cramps

SUGGESTED TEXTBOOKS

1.

2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.


THANK
YOU